REMARKS

FORMAL MATTERS:

Claims 16-18, 22-26, 30-34, 36 and 39-56 are pending after entry of the amendments set forth herein.

Claim 16, 24, and 30 have been amended. Support for these amendments is found in the claims as originally filed and throughout the specification at, for example, page 5, lines 8-13, and page 20, lines 27-28.

No new matter has been added.

REJECTIONS UNDER §112, ¶1 (ENABLEMENT)

The Office Action maintains the rejection of Claims 16-18, 22-26, 30-34 and 36 under 35 U.S.C. § 112, 1st ¶ for an asserted lack of enablement. This rejection is respectfully traversed.

In particular, the Office Action states that the specification is enabling for a method for directing the biodistribution of a drug that binds to a protein target by administering to a mammalian host a bifunctional molecule comprising a targeting moiety and a drug moiety, wherein the targeting moiety is a peptidyl-prolyl isomerase ligand for FKBP or cyclophilin selected from the group consisting of FK506, rapamycin and cyclosporine.

With respect to the targeting moiety, without conceding as to the correctness of the rejection and in the spirit of expediting prosecution, the claims have been amended to recite "said targeting moiety has an affinity for its intracellular protein of at least about 10^{-6} M".

The Applicants stress that the claims are not directed to all possible targeting molecules but specifically, those targeting molecules that (1) when in complex with a drug moiety with or without an optional linker moiety, the complex as a whole does not exceed 5000 daltons, and (2) have an affinity for their intracellular protein of at least about 10^{-6} M. Such language provides sufficient and coordinated structural and functional limitations (size and affinity) for the targeting moieties suitable for use in the claimed invention. Such limitation serves to distinguish

what is claimed from other targets and binding interactions, and furthermore can be coupled with assays which are well known and routine in this field.

The specification discloses illustrative examples of targeting moieties that are suitable for use with the subject invention; however the invention is not limited to these representative examples. The exemplary ligands described in the specification have common characteristics that enable them to be used in the bifunctional molecules of the present invention. Such characteristics include, size, affinity to a specific target present in a host, and are capable of targeting a protein present in the host at an elevated level, as claimed. Accordingly, other targeting moieties having the same size and affinity characteristics would reasonably be expected, by those in the art, to also function in a similar manner to the exemplary ligands described in the specification. Stated another way, the examples are believed to be sufficiently representative of the claimed genus, and show proof-of-concept experiments which support the claimed bifunctional approach.

Furthermore, the Applicants maintain that the present application provides sufficient disclosure to enable the invention to the full scope of the pending claims. The present specification clearly provides extensive description of the bifunctional molecules employed in the subject methods beginning at page 4 of the specification. This includes a generic description of these molecules, a detailed description of these molecules in terms of formulas, an extensive description of each of the component parts of the molecules, e.g., drug moieties (see pages 6 to 16), targeting moieties (see pages 16 to 21) and linking moieties (see pages 22 to 23). The number, kind and quality of these examples is sufficient to support the generic claims, particularly as amended.

In addition, a detailed description of how to make the targeted bifunctional molecules is provided at pages 24 to 28 of the specification, where specific guidance is provided on how to make the compounds. Three representative methods of making the compounds are described. Furthermore, page 26 provides even more detail regarding bifunctional molecules of the invention that include a peptidyl-prolyl isomerase-targeting moiety.

Guidance on how to screen candidate bifunctional molecules for suitability of use in the claimed methods is provided on page 25. In addition, page 29 of the specification provides an extensive description on how to use the bifunctional molecules in various applications, including dosages and administration routes, types of hosts, types of conditions, etc. While such screening does involve some experimentation, it is not undue, and is within the reasonable expectation of success of a person of ordinary skill in the art. The basic techniques are well-known, and their application to the present invention is described. Here, there is clear guidance as to the fundamental structural and functional requirements for a bifunctional molecule as claimed, and a reasonable expectation of success.

Therefore, the Applicants maintain that the methods disclosed in the present specification in conjunction with the knowledge available in the art at the time the present application was filed, would enable one of ordinary skill in the art to practice the invention to the full scope of the pending claims.

Moreover, the claims of the application do not require a therapeutic result be achieved upon administration of the bi-functional molecules. Rather, the claims only require that a biodistribution of a drug be directed to an intracellular space. Therefore, the concerns that are cited in the Office Action, with respect to treatment and disease condition are not relevant to claims directed to biodistribution of a drug to an intracellular space upon administration to a mammalian host. Furthermore, the specification provides ample disclosure with respect to use of the bifunctional molecules for inhibiting a binding event.

In sum, the amount of experimentation required to subject invention would not be undue and excessive because working examples have been provided, guidance is given on how to generate such compounds, and one of skill in the art would be able to perform the experiments as a matter of routine. The specification therefore provides sufficient enablement such that one of ordinary skill in the art would be able to practice the invention without undue experimentation. Accordingly, the specification clearly enables the subject invention as demonstrated in view of

the remarks presented herein and in view of the relevant *Wands* factors, as applied in the response filed on December 23, 2004.

In view of the above, it is respectfully submitted that Claims 16-18, 22-26, 30-34 and 36 are fully enabled under 35 U.S.C. § 112, 1st ¶ and that this rejection may be withdrawn.

REJECTIONS UNDER §102

Forsgren et al. (Office Action, page 7)

Claims 24 and 26 have been rejected under 35 U.S.C. §102(b) for allegedly being anticipated by Forsgren et al. (Cancer Res., 39(12):5155-5164 (1979)) as evident by Asai et al. (Acta Endocrinol., 87(1):173-180 (1978)). In view of the remarks made herein, this rejection may be withdrawn.

Claims 24 and 26 are directed to methods for modulating biodistribution of a drug to an **intracellular** space in a host by administering to the host a bifunctional molecule consisting of a drug moiety and a targeting moiety, **wherein both of drug moiety and the targeting moiety bind to intracellular proteins**. In other words, the drug moiety and the targeting moiety bind to proteins that exist **within** a cell.

In contrast, Forsgren et al. discloses the binding characteristics of a rat protein that binds estramustine phosphate. In particular, the cited reference discloses that the binding protein for estramustine is a "**secretory protein** formed in the prostate cell and transported into the lumen of the prostate lobulus" (see column 2, last paragraph, page 5162). Accordingly, Forsgren et al. discloses that estramustine phosphate binds to an **extracellular protein target, not an intracellular protein target**. Since Forsgren et al., discloses a compound that bind to a secreted protein that exists in the space outside of a cell, the cited reference fails to anticipate a method of using a bifunctional compound consisting of a targeting moiety that binds to an intracellular protein target that is on the inside of a cell.

It is well established that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 2 USPQ 2d 1051, 1053 (Fed. Cir. 1987), cert. denied, 481 U.S. 1052 (1987). See also, Scripps Clinic and Research Foundation v. Genentech, Inc., 18 USPQ 2d 1001 (Fed. Cir. 1991).

Since the cited reference fails to teach each and every element as recited in the pending claims, the cited reference fails to anticipate Claims 24-26. Accordingly, the Applicants respectfully request that this rejection be withdrawn.

Szepeshazi et al. (office Action, page 7)

The Office Action has maintained the rejection of Claims 16-18, 22-26, 30-34, and 36 under 35 U.S.C. § 102(b) for allegedly being anticipated by Szepeshazi et al. (Anticancer Drugs 8(10):974-987 (1997)) as evident by Nagy et al. (PNAS 93:2464-2469 (1996)), and Nagy et al. (PNAS 93:7269-7273 (1996)). In view of the remarks made herein, this rejection may be withdrawn.

The rejected claims of the present application are directed to methods for directing the biodistribution of a drug to an **intracellular** space in a host by administering to the host a bifunctional molecule consisting of a drug moiety and a targeting moiety, **wherein the targeting moiety that has an affinity for an intracellular protein**. In other words, the targeting moiety has an affinity to a target protein that exists **within** a cell.

In contrast, Szepeshazi et al. discloses a series of compounds comprising doxorubicin and luteinizing hormone releasing hormone (LH-RH), wherein the compounds are targeted to the LH-RH cell surface receptor. The Office Action incorrectly characterizes the LH-RH receptors as being located in the intracellular space; however, LH-RH receptors are located on the cell membrane in the extracellular space (e.g., outside of the cell), not the intracellular space – inside the cell (see discussion of LH-RH receptor levels beginning in column 2, page 980).

Therefore, since Szepeshazi et al., discloses a compound that bind to a cell surface protein that exists in the space outside of a cell, the cited reference fails to anticipate a method of using a bifunctional compound consisting a targeting moiety that has an affinity for an intracellular protein target that is on the inside of a cell.

As such, the cited reference fails to teach each and every element as recited in the pending claims. Thus, the Applicants respectfully request that this rejection be withdrawn.

REJECTIONS UNDER §103(A)

Forsgren et al., Asia et al., Trouet et al. (Office Action, page 10)

Claims 24 and 25 have been rejected under 35 U.S.C. §103(a) for allegedly being unpatentable over Forsgren et al. (Cancer Res., 39(12):5155-5164 (1979)) as evident by Asai et al. (Acta Endocrinol., 87(1):173-180 (1978)), in view of Trouet et al., (PNAS, 79:626-629 (1982)). In view of the remarks made herein, this rejection may be withdrawn.

As noted above, with respect to the rejection of claims 24-25 under §102(b), Forsgren et al. discloses that the binding protein for estramustine is a "**secretory protein** formed in the prostate cell and transported into the lumen of the prostate lobulus" (see column 2, last paragraph, page 5162). Accordingly, Forsgren et al. discloses that estramustine phosphate binds to an **extracellular protein target, not an intracellular protein target**. Forsgren et al. does not teach or suggest use of a bifunctional compound consisting of a targeting moiety that binds to an intracellular protein target that is on the inside of a cell.

Since Trouet et al. has been cited solely for its disclosure of a linking group, it fails to make up the deficiency of Forgren et al., as detailed above. Therefore, since the combination of the references do not teach each and every element found in the claims, the combination of the cited references fails to render the present claims obvious. Accordingly, the Applicants respectfully request that this rejection be withdrawn.

Forsgren et al., and WO 95/02684 (Office Action, page 10)

Claims 16-18, 22-23, 30-34, 36, and 39-56 have been rejected under 35 U.S.C. §103(a) for allegedly being unpatentable over Forsgren et al. (Cancer Res., 39(12):5155-5164 (1979)), in view of WO 95/02684. In view of the remarks made herein, this rejection may be withdrawn.

As will be shown below, the Examiner's rejection is deficient for at least the reason that the references fail to teach each and every limitation found in the claims. In particular, the cited references alone or in combination fail to teach a method for directing the biodistribution of a drug, by administering a bifunctional molecule **having a molecular weight that does not exceed 5 kDa**.

The law is clear that to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones,* 21 USPQ2d 1941 (Fed. Cir. 1992). Second, there must be a reasonable expectation of success. *In re Merck & Co., Inc.*, 231 USPQ 375 (Fed. Cir. 1986). Third, **the prior art reference, or references when combined, must teach or suggest all the claim limitations**. *In re Royka*, 180 USPQ 580 (CCPA 1974).

In making the rejection, the Office Action asserts that it would have been obvious "to substitute the estrogen targeting moiety as taught by Forsgren et al for the targeting moiety such as peptidyl-prolyl isomerase ligand FK506 type ligand, cyclosporine and rampamycin ...as taught by the WO 95/02684 (Office Action, page 12). However, the Applicants respectfully disagree.

In particular, the Applicants stress that WO 95/02684 teaches **large** chimeric proteins that comprise a targeting domain and an action domain (see page 4, lines 22-30). The cited reference further teaches that the targeting domains of such **large** chimeric proteins are "capable of **binding to** FK-506-type ligand, a cyclosporine A-type ligand, tetracycline or a steroid ligand"

that are present in a cell and are referred to in the cited reference as oligomerization ligands (see page 4, lines 31-35, emphasis added). Therefore, the cited reference does not teach a moiety such as a peptidyl-prolyl isomerase ligand FK506 type ligand, cyclosporine and rampamycin as a targeting domain of a chimeric molecule, but instead teaches that such molecules can be **targeted**, wherein such molecules are present in the cell. In other words, the reference refers to receptors such FK506, and does not use ligands to those receptors for constructing bifunctional molecules (ligand plus drug) as claimed.

For example, the cited reference provides in page 31, lines 1-3, that such a domain can be a FKBP and a cyclophilin **receptor** – not the ligand of such a receptor, as incorrectly stated in the Office Action. **In addition, the cited reference further states that such a domain will be on the order of 25 kDa** (see page 31, line 10). The 5 kDa size limitation referred to in the Office Action actually refers to the ligands present in the cell. For example, the cited reference provides that such an oligomerization ligand is "preferably a non-protein and has a molecule weight of less than about 5 kDa" (see page 4, line 12). Therefore, contrary to the Office Action, the combined teaching of the cited references does not provide for a bifunctional molecule comprising the nitrogen mustard domain of Forsgren et al. and a targeting domain **having a molecular weight that does not exceed 5 kDa**. Respectfully, the rejection appears to be based on an out-of-context reading of the references, based on hindsight from the present invention.

As such, the combination of the references fails to teach each and every limitation found in the claims of the present invention. Therefore, the cited references cannot render the present application obvious. As such, the Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-131.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: August 19, 2005

By: _____
Edward J. Baba
Registration No. 52,581

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue, Suite 200
East Palo Alto, California 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

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